THE COUNCIL FOR TOBACCO RESEARCH–U.S.A., INC.
110 EAST 59TH STREET
NEW YORK, N. Y. 10022
(212) 421-8885

Application for Research Grant
(Use extra pages as needed)

Date: July 17, 1973

1. Principal Investigator (give title and degrees):

Charles R. Shaw, M.D.
Biologist; Chief, Section of Medical Genetics
and Professor of Biology

2. Institution & address:

The University of Texas at Houston
M. D. Anderson Hospital and Tumor Institute
6723 Bertner Avenue
Houston, Texas 77025

3. Department(s) where research will be done or collaboration provided:

Department of Biology, Section of Medical Genetics

4. Short title of study:

Hydrocarbon Metabolizing Enzymes and Lung Cancer

5. Proposed starting date: January 1, 1974

6. Estimated time to complete: Three (3) years

7. Brief description of specific research aims:

a) To clarify the relationships between the variations in the human population of certain of the carcinogen-metabolizing enzymes and the occurrence of lung cancer.

b) To modify the method, developed in our laboratory, for assay of aryl hydrocarbon hydroxylase in human subjects, for adaptation as a clinical laboratory procedure.

c) To compare activities of these carcinogen-metabolizing enzymes in lung, cultured lymphocytes, and other tissues.

d) To investigate the effects of inherently different levels of these enzymes on rates of incorporation of carcinogen metabolites into cell components and the effects of these metabolites on cell activities, particularly DNA repair mechanisms and *in vitro* transformation.

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8. Brief statement of working hypothesis:

Most of the hydrocarbon carcinogens are converted in the target cell to the reactive epoxide form of the molecule, by aryl hydrocarbon hydroxylases (AHH). This is an inducible enzyme, and the degree of inducibility is genetically variable in man. We hypothesize that the level of AHH determines, at least in part, susceptibility to chemical carcinogenesis. Our preliminary studies in man support this hypothesis.

9. Details of experimental design and procedures (append extra pages as necessary)

The basic design of the clinical research is to measure AHH activity and inducibility in lung cancer subjects and their families, employing the lymphocyte culture system developed in our laboratory (Busbee *et al.*, 1972). This assay has been shown to be a competent indicaton of the general, hereditarily-determined inducibility of this enzyme in the individual. In the normal population there are three distinct groups, having low, intermediate, and high levels of inducibility (Kellermann *et al.*, 1973a). Preliminary studies of fifty lung cancer cases indicate that only persons with intermediate and high levels are susceptible to this disease. Larger and more detailed studies are indicated, to determine if those with highest AHH activities are more susceptible than intermediates (earlier onset, greater severity of disease, etc.), and which types of bronchogenic carcinoma are effected through the AHH system. It appears that the oat cell carcinoma is in a different category. Family studies of the lung cancer subjects are indicated, to clarify cause-effect relationships. Such studies will show whether the subjects fall into the expected hereditary groups, or whether their increased inducibility could be a result of the cancer. The latter is unlikely, but needs to be examined.

Lung tissue, both normal and diseased, will also be studied, by organ and tissue culture, to correlate enzyme activities with that in cultured lymphocytes. Other enzymes will also be studied in these tissues, particularly those which effect the breakdown of the epoxides and especially the epoxide hydrase. Preliminary studies in our laboratory suggest that the epoxide hydrase is not a rate-limiting enzyme in hydrocarbon metabolism (Kellermann *et al.*, 1973b).

To investigate effects of varying levels of AHH activity in the cell, cell cultures will be established from subjects with low and high levels. Rate of incorporation of labeled hydrocarbon metabolites into these cultured cell lines will be determined, and if possible, localization of binding sites will be identified. Further, effects of incorporation of these metabolites on DNA repair mechanisms will be measured in collaboration with Dr. Roger Hewitt of this depantment. These studies will be directed mainly to previously characterized DNA repair enzymes.

Efforts will be made to develop the AHH assay system as standardized clinical laboratory procedure. This has a number of obvious applications: as a diagnostic tool, in mass screening procedures to determine susceptibility to lung cancer and possibly other chemically induced cancers, and to study gene frequencies among various human populations. Our studies indicate that approximately half of the people in the U.S. population having low AHH inducibility, carry an extremely low risk for lung cancer due to smoking. The higher-risk individuals may be identified and counselled appropriately.

10. Space and facilities available (when elsewhere than item 2 indicates, state location):

The laboratories of the principal investigator are located on the fifth floor of the Research Institute Wing of The University of Texas M. D. Anderson Hospital and Tumor Institute. They consist of five laboratories totaling 1,600 square feet, with a walk-in cold room and four adjoining offices. They are well equipped for general biochemistry, and major items include a Nuclear-Chicago Unilux IIA Scintillation Counter, two Gilford recording spectrophotometers (Models 2400 and 240), Beckman L-4 preparative ultracentrifuge, 12 complete sets of starch gel electrophoresis apparatus, two Sorvall RC-2 B refrigerated high speed centrifuges, an incubator, and a large amount of column chromatography apparatus.

Additionally available for our use located in adjoining areas of the Department of Biology are a glassware preparations room, a walk-in incubator, and a variety of other biochemical instruments available for part-time use. This includes an Aminco-Bowman spectrophotofluorometer, which is the main instrument employed in the present investigation.

The clinical facilities of the M. D. Anderson Hospital and Tumor Institute are available for this study. The M. D. Anderson Hospital and Tumor Institute is a categorical institution for the study and treatment of neoplastic diseases. It has approximately 300 inpatient beds, and an addition is presently under construction which will add another 300. Patients are seen by referral only and the outpatient clinic sees approximately 6,000 referrals annually.

11. Additional facilities required:

Our pressing need for this project is for several items of equipment. A spectrophotofluorometer is, as noted above, the instrument employed for measuring the hydroxylase activity. We are presently using an instrument in the laboratory of Dr. Roger Hewitt, and his instrument is heavily used and at times not available to us. A $CO_2$ incubator is needed for the organ and cell culture work. For preparation of lymphocytes and cell cultures a refrigerated centrifuge is required. A phase-optics microscope is needed to evaluate the condition of cultured cells and to count the cells before and after culture.

Otherwise, the present facilities and equipment are quite adequate for this project.

12. Biographical sketches of investigator(s) and other professional personnel (append):

Charles R. Shaw, M.D., Elroy Cantrell, Ph.D., and Gottfried Kellermann, Ph.D. (Please see attached)

13. Publications: (five most recent and pertinent of investigator(s); append list, and provide reprints if available).

Attached

## BIOGRAPHICAL SKETCH

*(Give the following information for all professional personnel listed on page 3, beginning with the Principal Investigator. Use continuation pages and follow the same general format for each person.)*

| NAME | TITLE | BIRTHDATE (Mo., Day, Yr.) |
|---|---|---|
| Charles Raymond Shaw | Biologist and Professor of Biology; Chief, Section of Medical Genetics | REDACTED |
| PLACE OF REDACTED (City and country) | PRESENT NATIONALITY (If non-U.S. citizen, indicate kind of visa and expiration date) R | SEX ☒ Male ☐ Female |

EDUCATION *(Begin with baccalaureate training and include postdoctoral)*

| INSTITUTION AND LOCATION | DEGREE | YEAR CONFERRED | SCIENTIFIC FIELD |
|---|---|---|---|
| Hanover College, Hanover, Indiana | None | | Pre Med |
| University of Alabama, Tuscaloosa, Alabama | None | | Medicine |
| New York University School of Medicine, New York, New York | M.D. | 1946 | Medicine |

HONORS

Gamma Sigma Pi
Diplomate, American Board of Psychiatry and Neurology
Sigma Xi

| MAJOR RESEARCH INTEREST | ROLE IN PROPOSED PROJECT |
|---|---|
| Mammalian Biochemical Genetics | Principal Investigator |

RESEARCH SUPPORT *(See instructions)* PENDING GRANTS:

NIH Research Grant #5-R01-GM-15597, Genetic and Comparative Studies of Enzymes
09-01-68 through 08-31-73, $267,000 (direct costs)
Support during current year 09-01-72 through 08-31-73, $58,000 (direct costs)
(up for competitive renewal)

NIH Research Grant #1 R01 CA 14196, Enzymatic Modification of Chemical Carcinogens
01-01-73 through 12-31-77, $282,018 (direct costs)
Support during first year, 01-01-73 through 12-31-74, $57,426 (direct costs)
(approved but not funded, being held in active file until 31 December 1973)

RESEARCH AND/OR PROFESSIONAL EXPERIENCE *(Starting with present position, list training and experience relevant to area of project. List all or most representative publications. Do not exceed 3 pages for each individual.)*

Chief, Section of Medical Genetics, Department of Biology, The University of Texas at Houston M. D. Anderson Hospital and Tumor Institute, Houston, Texas, 1968 - present.
Biologist and Professor of Biology, Department of Biology, The University of Texas at Houston M. D. Anderson Hospital and Tumor Institute, Houston, Texas, 1969 - present.
Member, Graduate Faculty, The University of Texas at Houston Graduate School of Biomedical Sciences, Houston, Texas, 1969 - present.
Member, Senior Faculty, Medical Genetics Center, The University of Texas at Houston Graduate School of Biomedical Sciences, Houston, Texas, 1972 - present.
Associate Biologist and Associate Professor of Biology, The University of Texas at Houston M. D. Anderson Hospital and Tumor Institute, Houston, Texas, 1967-69.
Director, Biological Research Unit, Hawthorn Center (children's psychiatric hospital), Northville, Michigan, 1958-67.
Senior Staff Child Psychiatrist, Hawthorn Center, Northville, Michigan, 1956-58.
Resident in Psychiatry, Neuropsychiatric Institute, University of Michigan Medical School Ann Arbor, Michigan, 1953-56.
Chief, Nutrition and Metabolism Section, Arctic Aeromedical Laboratory, Fairbanks, Alaska, 1951-53.
Assistant Professor of Nutrition, Cornell University School of Nutrition, Ithaca, New York, 1949-51.
Resident, Internal Medicine, Cornell Infirmary and Memorial Hospital, Ithaca, New York, 1947-49.
Member: Am. Soc. Human Genet., Am. Psychiatric Assoc., Environmental Mutagen Soc., Genet. Soc. Am., Am. Soc. Zool., Aircraft Owners and Pilots Assoc.

PUBLICATIONS - Dr. Charles R. Shaw

Shaw, C. R. and E. Barto: Genetic Evidence for the Subunit Structure of Lactate Dehydrogenase Isozymes. Proc. Nat. Acad. Sci. U.S. 50: 211, 1963.

Koen, A. L. and C. R. Shaw: Multiple Substrate Specificities of Some Dehydrogenase Molecules. Biochem. Biophys. Res. Comm. 15: 92, 1964.

Shaw, C. R.: The Use of Genetic Variants in the Analysis of Isozyme Structure. Proc Brookhaven Symposia in Biology 17: 117, 1964.

Koen, A. L. and C. R. Shaw: A Preparative Method Employing Starch Gel Electrophoresis and Electrodialysis. Analyt. Biochem. 9: 495, 1964.

Shaw, C. R. and A. L. Koen: Aspartate Dehydrogenase Activity of Malate Dehydrogenase Biochim. Biophys. Acta 92: 397, 1964.

Shaw, C. R. and E. Barto: Autosomally Determined Polymorphism of Glucose-6-Phosphate Dehydrogenase in Peromyscus. Science 148: 1099, 1965.

Shaw, C. R.: Electrophoretic Variation in Enzymes. (lead article) Science 149: 936, 1965.

Shaw, C. R.: Glucose-6-Phosphate Dehydrogenase: Homologous Molecules in Deer Mouse and Man. Science 153: 1013, 1966.

Shaw, C. R. and A. L. Koen: Galactose Dehydrogenase, "Nothing" Dehydrogenase and Alcohol Dehydrogenase: Interrelation. Science 156: 3781, 1967.

Shaw, C. R. and A. L. Koen: Tissue-Specific Variation in Glucose-6-Phosphate Dehydrogenase Isozymes of Man and Deer Mouse. Ann. N. Y. Acad. Sci. 151: 149, 1968.

Shaw, C. R.: Isozymes: Classification, Frequency and Significance. Int'l. Rev. Cytol. 25: 297, 1969.

Shaw, C. R.: The Molecular Basis of Isozymes. Jap. J. Genet. 44, Suppl. 1: 31, 1969.

Wright, D. and C. R. Shaw: Genetics and Ontogeny of α-Glycerophosphate Dehydrogenase Isozymes of Drosophila melanogaster. Biochem. Genet. 3: 343, 1969.

Baptist, J., C. R. Shaw, and M. Mandel: Zone Electrophoresis of Enzymes in Bacterial Taxonomy. J. Bacteriol. 99: 180, 1969.

Shaw, C. R.: How Many Genes Evolve? Biochem. Genet. 4: 275, 1970.

Shaw, C. R. and R. Prasad: Starch Gel Electrophoresis of Enzymes--A Compilation of Recipes. Biochem. Genet. 4: 297, 1970.

Wright, D. A. and C. R. Shaw: Time of Expression of Genes Controlling Specific Enzymes in Drosophila Embryos. Biochem. Genet. 4: 385, 1970.

Busbee, D. L., C. R. Shaw, and E. T. Cantrell: Aryl Hydrocarbon Hydroxylase Induction in Human Leukocytes. Science 178: 315, 1972.

Nevo, Eviatar and Charles R. Shaw: Genetic Variation in a Subterranean Mammal, Spalax ehrenbergi. Biochem. Genet. 7: 235, 1972

DO NOT TYPE IN THE SPACE-BINDING MARGIN

Shaw, C. R., M. J. Siciliano, and D. A. Wright: Inter- and Intra-specific Genetic Distances Among Teleosts. Proc. Int'l. Cong. Zool., 1972, in press.

Stout, Daniel L. and Charles R. Shaw: Comparative Enzyme Patterns in Two Species of Thamnidium. Mycologia, in press.

Shaw, C. R.: Human Biochemical Variation. In Human Behavior Genetics, ed. A. R. Kaplan, M.D., in press.

Shaw, C. R. and R. Prasad: Genetic Variants of Enzymes Detectable by Zone Electrophoresis. In Handbook of Genetics, ed. Dr. R. C. King, Van Nostrand Reinhold Co., New York, in press.

Shaw, C. R., J. N. Baptist, D. A. Wright, and T. S. Matney: Induction of a Mutation in E. coli Affecting the Electrophoretic Mobility of Enzymes. Mutation Research 18: 247, 1973.

Kellermann, G., E. Cantrell, and C. Shaw: Variation in Inducibility of Aryl Hydrocarbon Hydroxylase in Human Leukocytes. Cancer Research, in press.

Kellermann, G., M. Luyten-Kellermann, and C. R. Shaw: Genetic Variation of Aryl hydrocarbon hydroxylase in Human Lymphocytes. American Journal of Human Genetics 25: 327, 1973.

Kellermann, G., M. Luyten-Kellermann, and C. R. Shaw: Presence and Induction of Epoxide Hydrase in Cultured Human Leukocytes. Biochemical and Biophysical Research Communications 52: 712, 1973.

Kellermann, G., M. Luyten-Kellermann, and C. R. Shaw: Metabolism of Polycyclic Aromatic Hydrocarbons in Cultured Human Leukocytes under Genetic Control. Submitted to Humangenetik.

Kellermann, G., C. R. Shaw, and M. Luyten-Kellermann: Aryl Hydrocarbon Hydroxylase Inducibility and Bronchogenic Carcinoma. Submitted to The New England Journal of Medicine.

## BIOGRAPHICAL SKETCH

*(Give the following information for all professional personnel listed on page 3, beginning with the Principal Investigator. Use continuation pages and follow the same general format for each person.)*

| NAME | TITLE | BIRTHDATE (Mo., Day, Yr.) |
|---|---|---|
| Elroy Taylor Cantrell | Research Associate | REDACTED |

| PLACE OF BIRTH (City, State, Country) | PRESENT NATIONALITY (If non-U.S. citizen, indicate kind of visa and expiration date) | SEX |
|---|---|---|
| REDACTED | REDACTED | ☒ Male ☐ Female |

EDUCATION *(Begin with baccalaureate training and include postdoctoral)*

| INSTITUTION AND LOCATION | DEGREE | YEAR CONFERRED | SCIENTIFIC FIELD |
|---|---|---|---|
| Arkansas State University, Jonesboro, Ark | B.S. | 1965 | Biology (chemistry) |
| University of Tennessee Medical Units, Memphis, Tennessee | M.S. | 1968 | Pharmacology |
| Baylor College of Medicine, Houston, Texas | Ph.D. | 1972 | Pharmacology(cell biolo |
| Baylor College of Medicine, Houston, Texas | | | Postdoctoral Fellow |

HONORS

Phi Eta Sigma - Arkansas State University
Honors System - Arkansas State University
Beta Beta Beta - Arkansas State Univeristy

| MAJOR RESEARCH INTEREST | ROLE IN PROPOSED PROJECT |
|---|---|
| Metabolism of carcinogens | Research Associate |

RESEARCH SUPPORT *(See instructions)*

RESEARCH AND/OR PROFESSIONAL EXPERIENCE *(Starting with present position, list training and experience relevant to area of project. List all or most representative publications. Do not exceed 3 pages for each individual.)*

Research Associate, The University of Texas Graduate School of Biomedical Sciences Medical Genetics Center, Houston, Texas, August, 1972 to present.

Postdoctoral Fellow. Studies of effect of Flavin deficiency on drug metabolism, studies of benzpyrene metabolism in human leukocytes and human pulmonary alveolar macrophages. Studies of effects of antimetabolites on components of mixed-function oxidases and enzyme activities. October 1971 - July, 1972.

Graduate student. Isolation of cell types in liver to study contribution of each in drug metabolism. Histofluorescence analysis for drug metabolism. Analysis of cytochromes $b_5$ and P-450 in hepatocytes and Kupffer cells. Some experience in electron microscopy, mass spectrometry, tissue culture, disc gel electrophoresis, and animal surgery. September, 1968 - October, 1971.

Graduate student. Studies of functional dynamics of the reticuloendothelial system and its relationship to drug metabolism. September, 1965 - September, 1968.

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PUBLICATIONS - Dr. Elroy Cantrell

Cantrell, Elroy T.: Induction of benzpyrene hydroxylase in parenchymal and Kupffer cells of rat liver. Ph.D. Dissertation, Department of Pharmacology, Baylor College of Medicine, Houston, Texas. 1971.

Cantrell, E., and Bresnick, E.: Evidence for type II enzyme induction by β-naptho-flavone. Life Sci. 10: 1195, 1971.

Cantrell, E. and Bresnick, E.: Benzpyrene hydroxylase activity in parenchymal and non-parenchymal cells of rat liver. J. Cell. Biol. 52: 316, 1972.

Cantrell, E. T., Martin, R. R., Warr, G. A., Busbee, D. L., Kellermann, G., and Shaw, C. R.: Induction of aryl hydrocarbon hydroxylase in human pulmonary alveolar macrophages by cigarette smoking. Submitted for publication, 1972.

Cantrell, E. T., Busbee, D. L., Kellermann, G., and Shaw, C. R.: Effects of mitogens and 3-methylcholanthrene on aryl hydrocarbons hydroxylase in cultured human lymphocytes. In preparation, 1972.

Black, O., Cantrell, E., Buccino, R. J., and Bresnick, E.: Effects of 3-methylcholanthrene administration on the proteins of endoplasmic reticulum. Biochem. Pharmacol. 20: 2989, 1971.

Busbee, D. L., Shaw, C. R., and Cantrell, E. T.: Aryl hydrocarbon hydroxylase induction in human leukocytes. Science 178: 315, 1972.

Kellermann, G., Cantrell, E., and Shaw, C. R.: Variation in inducibility of aryl hydrocarbon hydroxylase in human leukocytes. Submitted to Cancer Research.

Abstracts:

Cantrell, E. R., Cantrell, W. F., and Elko, E. E.: Sulfadiazine acetylation and phagocytic activity during liver regeneration in the rat. Pharmacologist 10: 191, 1968.

Cantrell, E. T., Burki, K., and Bresnick, E.: In vitro elevation of benzpyrene hydroxylase activity by 3-methylcholanthrene in rat hepatocytes. Southwest Section American Association for Cancer Research, October 16-17, 1970.

Cantrell, E.: Benzpyrene hydroxylase induction in parenchymal and non-parenchymal cells of rat liver. Fed. Proc. 30: 506, 1971.

Cantrell, E. and Busbee, D.: Benzpyrene hydroxylase in circulating leukocytes after exposure to polycyclic hydrocarbons. Fifth International Congress on Pharmacology. San Francisco, July 23-28, 1972.

Cantrell, E., Martin, R., Warr, G., and Shaw, C. R.: Aryl hydrocarbon hydroxylase induction in human alveolar macrophages. Clirical Research XX(4): 708, 1972.

Gerber, N., Seibert, R., Desiderio, D., Cantrell, E., and Lane, M.: Methodology for identification and quantification of 3,5-diamino-1,2,4-triazole, Guanazole (G), a new anticancer agent, and metabolic studies in man and animals. Fed. Proc. 31: 535 abs, 1972.

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## BIOGRAPHICAL SKETCH

*(Give the following information for all professional personnel listed on page 3, beginning with the Principal Investigator. Use continuation pages and follow the same general format for each person.)*

| NAME | TITLE | BIRTHDATE (Mo., Day, Yr.) |
|---|---|---|
| Gottfried H. Kellermann | Postdoctoral Fellow in Biology | REDACTED |
| PLACE OF BIRTH (City, State, Country) | PRESENT NATIONALITY (If U.S. citizen, indicate kind of visa and [illegible] if alien) | SEX |
| REDACTED | REDACTED | ☒ Male ☐ Female |

EDUCATION *(Begin with Baccalaureate or other initial professional education, such as Postdoctoral)*

| INSTITUTION AND LOCATION | DEGREE | YEAR CONFERRED | SCIENTIFIC FIELD |
|---|---|---|---|
| Philosophische Hochschule, Munich, Germany | M.S. | 1967 | Philosophy |
| University Frankfort, Mainz, Germany | M.S. | 1968 | Biology |
| University of Mainz, Germany | Ph.D. | 1971 | Human Genetics |
| University of Texas at Houston, M. D. Anderson Hospital and Tumor Institute | Postdoctoral Fellow | 1972 to present | Biochemical Genetic |

HONORS

Cum Laude, Philosophische Hochschule, Munich, Germany
Magna Cum Laude, University of Mainz, Faculty of Natural Sciences.

| MAJOR RESEARCH INTEREST | ROLE IN PROPOSED PROJECT |
|---|---|
| Biochemical Genetics | Research Associate |

RESEARCH SUPPORT *(See instructions)*

Fellowship, Deutsche Forschungsgemeinschaft (DFG) Grant KE 217, May 1972 through June, 1974.

RESEARCH AND/OR PROFESSIONAL EXPERIENCE *(Starting with present position, list training and experience relevant to area of project. List all or most representative publications. Do not exceed 3 pages for each individual.)*

Postdoctoral Fellow, The University of Texas at Houston, M. D. Anderson Hospital and Tumor Institute, Houston, Texas, 1972 to present.

Assistant Biologist, Anthropologisches Institute der Johannes Guternberg-Universitat, Mainz, Germany, 1971 to 1972.

Kellermann, G. and H. Walter: Investigation on the Population Genetics of the α1-Antiserum Polymorphisms. Humangenetik 10: 145-150, 1970.

Kellermann, G. and H. Walter: On the Genetics of the Pi-Serum Proteins. Humangenetik 10: 191-194, 1970.

Walter, H., M. Bajatzadeh, G. Kellermann, and T. Matznetter: Associations Between Leprosy and Serum Protein Groups. Humangenetik 10: 298-308, 1970.

Kellermann, G.: Methodological Investigations on the ABO-Typing of Ancient Bones. Humangenetik 14: 50-55, 1971.

Kellermann, G.: Further Studies on the ABO-Typing of Ancient Bones. Humangenetik 14: 232-236, 1972.

PUBLICATIONS - Dr. Gottfried Kellermann

Walter, H., G. Kellermann, M. Bajatzadeh, J. Krüger, and M. R. Chakravartti: Hp, Gc, Cp, Tj, Bg, and Pi-Phenotypes in Leprosy Patients and Healthy Controls from West Bengal (India). Humangenetik 14: 314-325, 1972.

Kellermann, G. and H. Walter: On the Population Genetics of the Ceruloplasmin Polymorphism. Humangenetik 15: 84-86, 1972.

Kellermann, G., E. Kleinman, and H. Walter: Zur Anwendbarkeit des Pi-Systems in der Vaterschaftskegutachtung Z. für Rechtsmedizin 71: 24-26, 1972.

Kellermann, G.: Paläoserologische Untersuchungen an Skelett funden aus dem 12. und 14. Jahrhundert. In press, 1973.

Kellermann, G., E. Cantrell, and C. Shaw: Variation in Inducibility of Aryl Hydrocarbon Hydroxylase in Human Leukocytes. Cancer Research, in press.

Kellermann, G., M. Luyten-Kellermann, and C. R. Shaw: Genetic Variation of Aryl Hydrocarbon Hydroxylase in Human Lymphocytes. American Journal of Human Genetics 25: 327, 1973.

Kellermann, G., M. Luyten-Kellermann, and C. R. Shaw: Presence and Induction of Epoxide Hydrase in Cultured Human Leukocytes. Biochemical and Biophysical Research Communications 52: 712, 1973.

Kellermann, G., M. Luyten-Kellermann, and C. R. Shaw: Metabolism of Polycyclic Aromatic Hydrocarbons in Cultured Human Leukocytes Under Genetic Control. Humangenetik, in press.

Kellermann, G., C. R. Shaw, and M. Luyten-Kellermann: Aryl Hydrocarbon Hydroxylase Inducibility and Bronchogenic Carcinoma. Submitted to The New England Journal of Medicine.

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13. Publications

a) Busbee, D. L., C. R. Shaw, and E. T. Cantrell: Aryl Hydrocarbon Hydroxylase Induction in Human Leukocytes. *Science 178:* 315-316, 1972.

b) Cantrell, E. T., R. R. Martin, G. A. Warr, D. L. Busbee, G. Kellermann, and C. Shaw: Induction of Aryl Hydrocarbon Hydroxylase in Human Pulmonary Alveolar Macrophages by Cigarette Smoking. *Transactions of the Association of American Physicians.* In press.

c) Kellermann, G., M. Luyten-Kellermann, and C. R. Shaw: Genetic Variation of Aryl Hydrocarbon Hydroxylase in Human Lymphocytes. *American Journal of Human Genetics 25:* 327-331, 1973.

d) Kellermann, G., M. Luyten-Kellermann, and C. R. Shaw: Presence and Induction of Epoxide Hydrase in Cultured Human Leukocytes. *Biochemical and Biophysical Research Communications 52:* 712-716, 1973.

e) Kellermann, G., C. R. Shaw, and M. Luyten-Kellermann: Aryl Hydrocarbon Hydroxylase Inducibility and Bronchogenic Carcinoma. Submitted to *The New England Journal of Medicine.*

(Reprints enclosed for publications a, c, and d. Preprints enclosed for publications b and e.)

14. First year budget:

| A. Salaries (give names or state "to be recruited") Professional (give % time of investigator(s) even if no salary requested) | % time | Amount |
|---|---|---|
| Charles R. Shaw, M.D. | | REDACTED |
| Elroy Cantrell, Ph.D. | | |
| Gottfried Kellermann, Ph.D. | | |
| Technical | | |
| To be recruited Research Technician III | | |
| To be recruited Research Technician II | | REDACTED |
| Fringe Benefits | | 1,529 |
| Sub-Total for A | | $ 20,301 |
| B. Consumable supplies (by major categories) | | |
| Chemicals | | $ 8,000 |
| Glassware | | 2,800 |
| Culture media | | 8,000 |
| Disposables | | 5,000 |
| Sub-Total for B | | $ 23,800 |
| C. Other expenses (itemize) | | |
| Volunteer human subjects: | | $ 5,200 |
| $10 x 400, blood specimens $ 4,000 | | |
| $35 x 20, pulmonary lavage 700 | | |
| $25 x 20, skin biopsy 500 | | |
| Travel, mostly local, to collect specimens from family members - private car and airplane | | 800 |
| Sub-Total for C | | $ 6,000 |
| Running Total of A + B + C | | $ 50,101 |
| D. Permanent equipment (itemize) | | |
| Spectrophotofluorometer, Aminco-Bowman, with ellipsoidel condensing system, XY recorder, extra cells and thin-film scanner | | $ 12,695 |
| Centrifuge, Beckman PR-J, with swinging bucket rotor | | 2,730 |
| Incubator, $CO_2$, New Brunswick Model CO-20 | | 1,350 |
| Microscope, Nikon, with phase optics and 35 mm. camera | | 2,330 |
| Sub-Total for D | | $ 19,105 |
| E. Indirect costs (15% of A+B+C) | | 7,515 |
| Total request | | $ 76,721 |

15. Estimated future requirements:
See attached

| | Salaries | Consumable Suppl. | Other Expenses | Permanent Equip. | Indirect Costs | Total |
|---|---|---|---|---|---|---|
| Year 2 | $ 21,311 | 24,500 | 6,500 | -0 | 7,847 | $ 60,158 |
| Year 3 | $ 22,288 | 25,000 | 7,000 | -0 | 8,143 | $ 62,431 |

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15. Estimated future requirements:

Personnel

Salaries are budgeted in accordance with the Institution's Personnel Pay Plan. Fringe Benefits include employer contributions to Social Security, Workmen's Compensation Insurance, Unemployment Compensation Insurance, and employee's insurance program. These costs are all uniformly charged as direct costs to all grants and contracts.

Increases requested for personnel in subsequent years have been computed in accordance with the established institutional policy, and include a one-step increase for all employees in all additional years of the project.

16. Other sources of financial support:
List financial support from all sources, including own institution, for this and related research projects.

CURRENTLY ACTIVE

| Title of Project | Source (give grant numbers) | Amount | Inclusive Dates |
|---|---|---|---|
| | | | |

PENDING OR PLANNED

| Title of Project | Source (give grant numbers) | Amount | Inclusive Dates |
|---|---|---|---|
| Genetic and Comparative Studies of Enzymes (up for competitive renewal) | National Institutes of Health #2 ROI GM 15597-07 | 346,840 | 09-01-73 through 08-31-78 |

It is understood that the investigator and institutional officers in applying for a grant have read and accept the Council's "Statement of Policy Containing Conditions and Terms Under Which Project Grants Are Made."

Principal investigator

Typed Name Charles R. Shaw, M.D.

Signature Charles R. Shaw Date 17 July 1973

Telephone 713 (Area Code) 526-5411 (Number) 522 (Extension)

Checks payable to:
Mr. E. R. Gilley, Business Manager

Mailing address for checks:
The University of Texas at Houston
M. D. Anderson Hospital and Tumor Institute
6723 Bertner Avenue
Houston, Texas 77025

Responsible officer of institution:

Typed Name Robert C. Hickey, M.D.

Title Director

Signature Robert C. Hickey Date 7/27/73

Telephone 713 526-5411 544

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